International Journal of Infectious Diseases (2008) **12**, 396—401

ELSEVIER

INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES

http://intl.elsevierhealth.com/journals/ijid

Efficacy of linezolid in the treatment of mediastinitis due to methicillin-resistant *Staphylococcus aureus*: an experimental study

Mustafa Sacar [a,*], Suzan Sacar [b], Ilknur Kaleli [c], Nural Cevahir [c], Zafer Teke [d], Semra Toprak Kavas [b], Ali Asan [b], Faruk Onder Aytekin [d], Ahmet Baltalarli [a], Huseyin Turgut [b]

[a] *Department of Cardiovascular Surgery, Pamukkale University Faculty of Medicine, Kinikli Kampusu, Kinikli 20070 Denizli, Turkey*
[b] *Department of Clinical Microbiology and Infectious Diseases, Pamukkale University Faculty of Medicine, Denizli, Turkey*
[c] *Department of Microbiology, Pamukkale University Faculty of Medicine, Denizli, Turkey*
[d] *Department of General Surgery, Pamukkale University Faculty of Medicine, Denizli, Turkey*

Received 18 June 2007; received in revised form 25 August 2007; accepted 17 September 2007
Corresponding Editor: Craig Lee, Ottawa, Canada

KEYWORDS
Linezolid;
Surgical site infection

Summary
Introduction: The treatment of postoperative mediastinitis is very important because of its high morbidity, mortality, and increased hospital stay and hospital costs. The aims of our research were to investigate whether linezolid alone can be an effective treatment agent for methicillin-resistant *Staphylococcus aureus* (MRSA) mediastinitis, and to determine whether linezolid can provide synergistic activity when given in combination with rifampin.
Methods: A partial upper median sternotomy was performed on 70 rats. The animals were divided into seven groups: an uncontaminated control group; an untreated contaminated group; three contaminated groups that received antibiotic therapy with either 25 or 50 mg/kg linezolid twice a day, or rifampin 5 mg/kg twice a day; and two contaminated groups that received a combination therapy consisting of 25 or 50 mg/kg linezolid and rifampin 5 mg/kg twice a day. The antibiotic treatment lasted 7 days. Tissue samples from the upper ends of the sternum and swab specimens of the upper mediastinum were obtained and evaluated microbiologically.
Results: The 25-mg/kg dose of linezolid, either alone or combined with rifampin, was not effective in reducing the bacterial counts in mediastinum and sternum. Quantitative bacterial cultures of mediastinum and sternum were significantly lower in the groups receiving 50 mg/kg linezolid alone or in combination with rifampin compared with the control. Adding of rifampin to linezolid therapy did not result in a significant change in bacterial counts versus linezolid alone.
Conclusion: A high dose of linezolid should be considered as a possible therapeutic agent for the treatment of post-sternotomy infection caused by MRSA.

* Corresponding author. Tel.: +90 258 2118585x2251; fax: +90 258 2410040.
E-mail address: mustafasacar@hotmail.com (M. Sacar).

1201-9712/$32.00
doi:10.1016/j.ijid.2007.09.017

Introduction

Although postoperative mediastinitis after open heart surgery is a rare complication, it is associated with a mortality of up to 47% and increased hospital stay and hospital costs.[1–3] Staphylococci are the main causative organisms, accounting for 54–79% of cases.[1,4] *Staphylococcus aureus* mediastinitis often occurs due to perioperative contamination of the mediastinal space.[2] Methicillin-resistant *Staphylococcus aureus* (MRSA) mediastinitis has been found to be associated with higher rates of overall mortality, mediastinitis-related death, and treatment failure.[5]

Optimal outcomes in post-surgical mediastinitis require surgical management in addition to systemic antibiotic therapy.[6–8] MRSA is showing an increasing prevalence worldwide and most strains are now also resistant to fluoroquinolones, macrolides, tetracyclines, and aminoglycosides.[9,10] Since the antibiotics used traditionally for the treatment of serious infections caused by these resistant staphylococci are limited, there is a requirement for new therapeutic approaches.

Linezolid is a synthetic oxazolidinone antimicrobial agent that has a good activity against most medically important Gram-positive microorganisms resistant to methicillin and vancomycin.[11,12] Recently dual or multi-drug combinations have been encouraged in the hope of preventing antibiotic resistance.[13,14] Rifampin is highly bactericidal towards *Staphylococcus* species.[15] Several trials of linezolid, alone or in combination with rifampin, have been published;[16–19] however, its efficacy and safety in mediastinitis are less well reported.

The aims of our research were to investigate whether linezolid alone can be an effective treatment agent for MRSA mediastinitis, and to determine whether linezolid can provide synergistic activity when given in combination with rifampin.

Methods

This study was approved by the local animal research ethics committee. During the entire study the animals were kept at our institution's animal research laboratory under veterinary supervision. All animals received human care in compliance with *Principles of laboratory animal care*, formulated by the *Guide for the care and use of laboratory animals*, prepared by the National Academy of Sciences.[20]

Organisms and susceptibility testing

The strain of MRSA used in this study was isolated from blood culture and a surgical site infection specimen from a patient with post-sternotomy mediastinitis following open heart surgery. Identification of the clinical isolates was determined by Gram staining, catalase reaction, tube coagulation test, and Api-Staph test (bioMérieux, Lyon, France). Methicillin sensitivity was investigated by oxacillin disk diffusion test.[21]

The antimicrobial susceptibility of the strain was determined by using the broth microdilution method, according to the procedures outlined by the Clinical and Laboratory Standards Institute specifications.[22,23] The minimum inhibitory concentration was taken to be the lowest antibiotic concentration at which observable growth was inhibited.

Drugs

Linezolid (Pfizer, Halden, Norway) and rifampin (Kocak Farma, Istanbul, Turkey) were diluted in accordance with the manufacturers' recommendations. Solutions of drugs were made fresh on the day of assay.

In vivo rat model

Seventy adult male Wistar rats weighing between 300 and 350 g were randomly divided into seven groups. There were 10 rats in each group. Group 1 was an uncontaminated control group with no contamination and no antibiotic therapy given; group 2 was an untreated contaminated control group with local MRSA contamination and no antibiotic therapy given; group 3 consisted of those with local MRSA contamination given intraperitoneal linezolid (25 mg/kg of body weight) twice a day; group 4 consisted of those with local MRSA contamination given intraperitoneal linezolid (50 mg/kg of body weight) twice a day; group 5 consisted of those with local MRSA contamination given intramuscular rifampin (5 mg/kg of body weight) twice a day; group 6 consisted of those with local MRSA contamination given intraperitoneal linezolid (25 mg/kg of body weight) and intramuscular rifampin (5 mg/kg of body weight) twice a day; group 7 consisted of those with local MRSA contamination given intraperitoneal linezolid (50 mg/kg of body weight) and intramuscular rifampin (5 mg/kg of body weight) twice a day.

Each rat was anesthetized intramuscularly with a 2:1 mixture of ketamine hydrochloride (100 mg/ml; Pfizer) and xylazine hydrochloride (20 mg/ml; Bayer) at a dose of 0.75 ml/kg. The hair on the rats' chests was shaved, the skin cleaned with 10% povidone-iodine solution, and a sterile towel was used to cover the sternum. The skin and presternal layers were incised. A partial upper median sternotomy without access to pleural spaces was performed on all rats. Groups 2–7 were inoculated with 0.5 ml 10^8 colony-forming units (CFU)/ml MRSA in the mediastinal and in the sternal layers. The sternum and the presternal layers were closed with a single 3-0 Prolene suture. Animals were returned to individual cages and examined thoroughly daily. During the treatment period no medication was given to the rats in groups 1 and 2. Postoperatively, groups 3–7 were given antibiotic treatment for seven days, twice daily, starting 24 hours after the end of the procedure. After 12 hours following the end of treatment, the rats were sacrificed, a sternotomy was performed for each rat, and tissue samples from the upper ends of the sternum and swab specimens of the upper mediastinum were aseptically obtained.

Assessment of the infection

Mediastinal swab specimens were placed in tubes containing 1 ml of phosphate-buffered saline solution and sonicated for 5 minutes. Quantitation of viable bacteria was performed by culturing serial 10-fold dilutions (0.1 ml) of the bacterial suspension on blood agar plates. All plates were incubated at 37 °C for 48 hours and evaluated for the presence of the staphylococcal strains. The organisms were quantitated by counting the number of CFU per plate. Tissue samples were weighed and homogenized under sterile conditions in 1 ml of sterile phosphate-buffered saline. The serial diluted homo-

genates were inoculated (0.01) onto blood agar and incubated at 37 °C. After 48 hours, the amount of growing bacteria was determined as CFU/g tissue.

Statistical analysis

Quantitative culture results were presented as arithmetic mean ± standard deviation (SD) of CFU. Differences among the groups were evaluated using one-way analysis of variance (ANOVA), and multiple comparisons between the groups were performed with a posthoc test (Tukey's HSD test). Differences were considered statistically significant when $p < 0.05$. Data were analyzed using statistical software SPSS for Windows 11.0 (SPSS, Chicago, IL, USA).

Results

According to the broth microdilution method, the clinical isolate was susceptible to linezolid and rifampin. The minimal inhibitory concentrations (MICs) for linezolid and rifampin in the strain of *S. aureus* used in this study were found to be 2 μg/ml and 0.5 μg/ml, respectively.

Evidence of mediastinitis was present in all rats of the untreated contaminated group. In contrast, none of the animals included in the uncontaminated control group had anatomic or microbiological evidence of mediastinitis. All the rats in the groups that received antibiotic treatment, except two rats in group 4 and a rat in group 7, showed evidence of infection. Culture negative rates and bacterial counts for each group are shown in Table 1.

The average growth of the microorganisms in the mediastinum and sternum were compared. The 25-mg/kg dose of linezolid, either alone or combined with rifampin, was not effective in reducing the bacterial counts in mediastinum and sternum in comparison with the contaminated untreated group ($p > 0.05$). Quantitative bacterial cultures of mediastinum and sternum were significantly lower in the groups receiving 50 mg/kg linezolid alone or in combination with rifampin (groups 4 and 7) when compared to the untreated contaminated group (group 2) and groups receiving 25 mg/kg linezolid, rifampin, or their combination (groups 3, 5, and 6; $p < 0.05$). However, there was no statistically significant difference in terms of mean bacterial counts between the 25 mg/kg linezolid monotherapy group and the 25 mg/kg linezolid plus rifampin group (group 6; $p > 0.05$). The same difference was also found between the 50 mg/kg linezolid monotherapy and rifampin combination groups. Finally, there was no mortality among the rats and we did not encounter any clinical evidence of drug-related adverse effects, such as local signs of perigraft inflammation, anorexia, vomiting, diarrhea, or alteration in behavior.

Discussion

In this study of experimental mediastinitis caused by MRSA, treatment with linezolid at 50 mg/kg was found to be effective in reducing the bacterial count in mediastinum and sternum, whereas the same efficacy was not observed at 25 mg/kg. The combination of linezolid and rifampin was not able to significantly change the treatment results when compared with those obtained with linezolid alone.

There are reports of several clinical and experimental studies of linezolid alone or in combination with rifampin;[16,17,24] however, its exact efficacy and safety in post-sternotomy mediastinitis have not been well reported. Jacqueline et al.[25] found that linezolid plus rifampin was the most active combination against MRSA strains in comparison with gentamicin and vancomycin in time–kill experiments. In vivo studies of the linezolid–rifampin combination in an MRSA bacteremia model and a methicillin-sensitive *S. aureus* (MSSA) endocarditis model have shown additivity or indifference.[18,19] The purpose of our study was to evaluate the efficacy of linezolid as a treatment agent for MRSA mediastinitis and to investigate whether linezolid can provide synergistic activity when given in combination with rifampin in the treatment of that serious infection. Based on prior experimental and clinical research on MRSA infections,[18,26–29] we developed an experimental mediastinitis model.

Table 1 Outcome of 7-day treatment of experimental mediastinitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA)

Group	Drug and dose	No. culture negative/total		Mean bacterial count	
		Swab	Sternum	Mediastinum[a]	Sternum[b]
Group 1 (Uncontaminated control)	No drug	10/10	10/10	0.0	0.0
Group 2 (Untreated contaminated control)	No drug	0/10	0/10	5.20 ± 0.15	5.59 ± 0.20
Group 3	Linezolid[c] (25)	0/10	0/10	4.68 ± 0.28	5.18 ± 0.20
Group 4	Linezolid[c] (50)	2/10	2/10	2.49 ± 1.32[e]	2.59 ± 1.38[f]
Group 5	Rifampin[d] (5)	0/10	0/10	4.87 ± 0.07	5.25 ± 0.20
Group 6	Linezolid[c] (25) + rifampin[d] (5)	0/10	0/10	4.85 ± 0.10	5.21 ± 0.19
Group 7	Linezolid[c] (50) + rifampin[d] (5)	1/10	1/10	2.97 ± 1.05[e]	3.06 ± 1.08[f]

[a] Log_{10}CFU/ml ± SD.
[b] Log_{10}CFU/g ± SD.
[c] Administered intraperitoneally twice daily.
[d] Administered intramuscularly twice daily.
[e] $p < 0.05$ vs. the mean bacterial counts of the mediastinum in groups 2, 3, 5, and 6.
[f] $p < 0.05$ vs. the mean bacterial counts of the sternum in groups 2, 3, 5, and 6.

In recent years the effectiveness of new antimicrobial agents has been widely investigated in cardiovascular infections. The increasing prevalence of MRSA in cardiac surgery units has led to increased vancomycin utilization for these serious and life-threatening infections seen in these units.[30–34] Since the emergence of glycopeptide intermediate and resistant *S. aureus*,[35,36] clinicians have understood the importance of minimizing glycopeptide use.

In order to choose a proper treatment and prevent unnecessary use of broad-spectrum antibiotics, an exact definition of post-sternotomy mediastinitis should rely on both clinical and bacteriological criteria. This is especially important with regard to infections caused by MRSA, as these infections have a comparatively worse clinical outcome.[5,37] Linezolid has been demonstrated to be effective in the clinical management of MRSA infections.[23,38,39] We investigated the activity of linezolid in an experimental model of mediastinitis due to MRSA, because analogous infections in humans are common in clinical practice and generally require aggressive surgical debridement and prolonged courses of systemic antimicrobial treatment.

The dose of linezolid was selected to mimic the therapeutic dose given to patients, and was also based on dose regimens used in other animal models of infection. A 25-mg/kg oral dose of linezolid in rats produces plasma exposures comparable to those obtained in humans following a 600-mg oral dose.[40–42] The approximately 100% bioavailability of linezolid allows the drug to be administered either parenterally or orally in the same dose without requiring a dose adjustment.[43] The excellent bioavailability of linezolid in rats has also been demonstrated.[28]

We used a normal dose and a higher dose, as our MRSA strain was less susceptible in vitro. For the same reason Jabes et al.[42] used linezolid at 50-, 100-, and 200-mg/kg doses once orally in rats infected with MRSA. Based on the pharmacokinetics of linezolid against the strain tested, they expected the dose of 50 mg/kg to be effective against MRSA. But this dose was found to be ineffective in reducing the bacterial load of the MRSA strain. A 100-mg/kg oral dose of linezolid was found to be necessary to achieve an adequate reduction in bacterial titer.

Oramas-Shirey et al.[44] reported that a 25-mg/kg intravenous dose of linezolid given three times a day for 5 days was not effective in the treatment of experimental staphylococcal endocarditis in a rabbit model, whereas doses of 50 or 75 mg/kg with the same treatment schedule were found to be effective.

The efficacy of linezolid at 50 mg/kg/day or 100 mg/kg/day in a rat model of pneumococcal pneumonia has also been evaluated, and the latter was found to be more effective.[25] As linezolid has not been extensively investigated in cardiovascular infections, and there have been reports of treatment failure in another serious cardiovascular infection endocarditis with the standard dose used in humans,[45] we decided to investigate the efficacy of linezolid at a double dose in mediastinitis and compare it with the standard dose. We found that linezolid at a double dose was effective in reducing the bacterial count in mediastinum and sternum. We did not observe any side effects with the high dose, but this requires confirmation in future studies in humans.

Additionally, our results demonstrated that adding rifampin to linezolid treatment did not change the results obtained with linezolid alone. This is especially important in practice, as clinicians should also minimize rifampin utilization in order to avoid rifampin resistance.

Linezolid at 50 mg/kg seemed to be an effective agent in our experimental mediastinitis model, and this result suggests that this antibiotic may be a reasonable therapeutic choice. Unfortunately, although the possibility of acquired resistance to linezolid is low, there are recent studies reporting a risk of linezolid resistance after exposure to this drug.[46–48] This is why it should be considered only for patients with serious MRSA infections that are poorly responsive to the glycopeptides or those who do not tolerate glycopeptide treatment.

More clinical studies are required on the combination of linezolid with other antimicrobial agents in order to increase the bactericidal activity of therapy, to prevent the emergence of drug-resistant subpopulations, and to provide a complementary antibacterial spectrum.

When considering our results, the following limitations of our study need to be taken into account. Our in vivo model used a direct form of MRSA inoculation in the mediastinal and in the sternal layers. Additionally, we did not determine serum antibiotic concentration in the rats. Unfortunately, the required technical equipment for measuring the antibiotic concentration is not present in our hospital as we live in a country with limited financial resources. We used linezolid in a dose that mimics the validated human dose and its double form, and investigated its efficacy by evaluating the presence and the amount of the staphylococcal strains in the infected area. However, the animal model in this study is not directly comparable with the real situation in a living human being.

In conclusion, linezolid at 25 mg/kg, rifampin, and the combination of linezolid at 25 mg/kg and rifampin did not significantly reduce the bacterial counts and were found to be ineffective in the treatment of our experimental mediastinitis model. The combination of rifampin with linezolid therapy did not result in a significant change in bacterial counts versus linezolid alone. Finally, increasing the dose of linezolid from 25 mg/kg to 50 mg/kg resulted in a significant reduction in bacterial counts. Based on our findings, high-dose linezolid should be considered as a possible therapeutic agent for the treatment of post-sternotomy infection caused by MRSA. Our results need to be confirmed in further preclinical and clinical studies.

Conflict of interest: No conflict of interest to declare.

References

1. Farinas MC, Gald Peralta F, Bernal JM, Rabasa JM, Revuelta JM, Gonzalez-Macias J. Suppurative mediastinitis after open-heart surgery: a case—control study covering a seven-year period in Santander, Spain. *Clin Infect Dis* 1995;**20**:272—9.
2. Gardlund B, Bitkover C, Vaage J. Postoperative mediastinitis in cardiac surgery—microbiology and pathogenesis. *Eur J Cardiothorac Surg* 2002;**21**:825—30.
3. Loop FD, Lytle BW, Cosgrove DM, Mahfood S, McHenry MC, Goormastic M, et al. Sternal wound complications after isolated coronary artery bypass grafting: early and late mortality, morbidity, and cost of care. *Ann Thorac Surg* 1990;**49**:179—86.
4. Munoz P, Menasalvas J, de Quiros B, Desco M, Vallejo J, Bouza E. Post-surgical mediastinitis: a case—control study. *Clin Infect Dis* 1997;**25**:1060—4.

5. Mekontso-Dessap A, Kirsch M, Brun-Buisson C, Loisance D. Post-sternotomy mediastinitis due to *Staphylococcus aureus*: comparison of methicillin-resistant and methicillin-susceptible cases. *Clin Infect Dis* 2001;**32**:877—83.
6. Rupp ME. Mediastinitis. In: Mandell GL, Bennet JE, Dolin R, editors. *Principles and practice of infectious diseases*. 6th ed. Philadelphia, Pennsylvania: Elsevier Churchill Livingstone; 2005. p. 1070—8.
7. De Feo M, Gregorio R, Della Corte A, Marra C, Amarelli C, Renzulli A, et al. Deep sternal wound infection: the role of early debridement surgery. *Eur J Cardiothorac Surg* 2001;**19**:811—6.
8. Losanoff JE, Richman BW, Jones JW. Disruption and infection of median sternotomy: a comprehensive review. *Eur J Cardiothorac Surg* 2002;**21**:831—9.
9. Schindler B. Worldwide spread of resistant Staphylococcus. *Med Monatsschr Pharm* 2007;**30**:155—6.
10. Santos Sanches I, Mato R, de Lencastre H, Tomasz A, CEM/NET Collaborators and the International Collaborators. Patterns of multidrug resistance among methicillin-resistant hospital isolates of coagulase-positive and coagulase-negative staphylococci collected in the international multicenter study RESIST in 1997 and 1998. *Microb Drug Resist* 2000;**6**:199—211.
11. Livermore DM. Linezolid in vitro: mechanism and antibacterial spectrum. *J Antimicrob Chemother* 2003;**51**:9—16.
12. Rybak MJ, Hershberger E, Moldovan T, Grucz RG. In vitro activities of daptomycin, vancomycin, linezolid, and quinupristin—dalfopristin against staphylococci and enterococci, including vancomycin-intermediate and -resistant strains. *Antimicrob Agents Chemother* 2000;**44**:1062—6.
13. Drlica K. A strategy for fighting antibiotic resistance. *ASM News* 2001;**67**:27—33.
14. Koleff MH, Fraser VJ. Antibiotic resistance in the intensive care unit. *Ann Intern Med* 2001;**134**:298—314.
15. Sano K, Tunakawa N. Chemistry of rifampicin. *Med Treatment* 1970;**23**:928—35.
16. Cepeda JA, Whitehouse T, Cooper B, Hails J, Jones K, Kwaku F, et al. Linezolid versus teicoplanin in the treatment of Gram-positive infections in the critically ill: a randomized, double-blind, multicentre study. *J Antimicrob Chemother* 2004;**53**:345—55.
17. Gander S, Hayward K, Finch R. An investigation of the antimicrobial effects of linezolid on bacterial biofilms utilizing an in vitro pharmacokinetic model. *J Antimicrob Chemother* 2002;**49**:301—8.
18. Dailey CF, Pagano PJ, Buchanan LV, Paquette JA, Haas JV, Gibson JK. Efficacy of linezolid plus rifampin in an experimental model of methicillin-susceptible *Staphylococcus aureus* endocarditis. *Antimicrob Agents Chemother* 2003;**47**:2655—8.
19. Ford CW, Hamel JC, Wilson DM, Moerman JK, Stapert D, Yancey Jr RJ et al. In vivo activities of U-100592 and U-10076, novel oxazolidinone antimicrobial agents, against experimental bacterial infections. *Antimicrob Agents Chemother* 1996;**40**:1508—13.
20. Institute of Laboratory Animal Resources National Research Council. *Guide for the care and use of laboratory animals*. Washington, DC: National Academy Press; 1996.
21. Kloos WE, Barnerman TL. Staphylococcus and micrococcus. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, editors. *Manual of clinical microbiology*. 7th ed. Washington: ASM Press; 1999. p. 264—77.
22. Clinical and Laboratory Standards Institute. *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard. M07-A7*. Wayne, PA: Clinical and Laboratory Standards Institute; 2006.
23. National Committee for Clinical Laboratory Standards. *Methods for determining bactericidal activity of antimicrobial agents; approved guideline. M26-A*. Wayne, PA: National Committee for Clinical Laboratory Standards; 1997.
24. Kruse AJ, Peerdeman SM, Bet PM, Debets-Ossenkopp YJ. Successful treatment with linezolid and rifampicin of meningitis due to methicillin-resistant *Staphylococcus epidermidis* refractory to vancomycin treatment. *Eur J Clin Microbiol Infect Dis* 2006;**25**:135—7.
25. Jacqueline C, Caillon J, Le Mabecque V, Miegeville AF, Donnio PY, Bugnon D, et al. In vitro activity of linezolid alone and in combination with gentamicin, vancomycin, or rifampicin against methicillin-resistant *Staphylococcus aureus* by time—kill curve methods. *J Antimicrob Chemother* 2003;**51**:857—64.
26. Ersoz G, Aytacoglu B, Sucu N, Tamer L, Bayindir I, Kose N, et al. Comparison and evaluation of experimental mediastinitis model: precolonized foreign body implants and bacterial suspension inoculation seems promising. *BMC Infect Dis* 2006;**6**:76.
27. Gentry-Nielsen MJ, Olsen KM, Preheim LC. Pharmacodynamic activity and efficacy of linezolid in a rat model of pneumococcal pneumonia. *Antimicrob Agents Chemother* 2002;**46**:1345—51.
28. Slatter JG, Adams LA, Bush EC, Chiba K, Daley-Yates PT, Feenstra KL, et al. Pharmacokinetics, toxicokinetics, distribution, metabolism and excretion of linezolid in mouse, rat and dog. *Xenobiotica* 2002;**32**:907—24.
29. Ogus TN, Hulusi Us M, Cicek S, Ozkan S, Yuksel Ozturk O, Isik O. Sternal cyanoacrylate gluing in mediastinitis. Effects on infection, stability and bone healing. *J Cardiovasc Surg (Torino)* 2002;**43**:741—6.
30. Combes A, Trouillet JL, Baudot J, Mokhtari M, Chastre J, Gibert C. Is it possible to cure mediastinitis in patients with major postcardiac surgery complications? *Ann Thorac Surg* 2001;**72**:1592—7.
31. Naylor AR, Hayes PD, Darke S. A prospective audit of complex wound and graft infections in Great Britain and Ireland: the emergence of MRSA. *Eur J Vasc Endovasc Surg* 2001;**21**:289—94.
32. Wilson WR, Karchmer AW, Dajani AS, Taubert KA, Bayer A, Kaye D, et al. Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. American Heart Association. *JAMA* 1995;**274**:1706—13.
33. Foville Jr RJ, Zaske DE, Kaplan EL, Crossley K, Sabath LD, Quie PG. *Staphylococcus aureus* endocarditis. Combined therapy with vancomycin and rifampin. *JAMA* 1978;**240**:1963—5.
34. Pallares R, Dick R, Wenzel RP, Adams JR, Nettleman MD. Trends in antimicrobial utilization at a tertiary teaching hospital during a 15-year period (1978—1992). *Infect Control Hosp Epidemiol* 1993;**14**:376—82.
35. Smith TL, Pearson ML, Wilcox KR, Cruz C, Lancaster MV, Robinson-Dunn B, et al. Emergence of vancomycin resistance in *Staphylococcus aureus*. Glycopeptide-Intermediate Staphylococcus aureus Working Group. *N Engl J Med* 1999;**340**:493—501.
36. Howden BP, Ward PB, Charles PG, Korman TM, Fuller A, du Cros P, et al. Treatment outcomes for serious infections caused by *Staphylococcus aureus* with reduced vancomycin susceptibility. *Clin Infect Dis* 2004;**38**:521—8.
37. Romero-Vivas J, Rubio M, Fernandez C, Picazo JJ. Mortality associated with nosocomial bacteremia due to methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis* 1995;**21**:1417—23.
38. Stevens DL, Herr D, Lampiris H, Hunt JL, Batts DH, Hafkin B. Linezolid versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. *Clin Infect Dis* 2002;**34**:1481—90.
39. Dresser JD, Birmingham MC, Karchmer AW, Rayner CR, Falvin SM, Schentag JJ. Results of treating infective endocarditis with linezolid [abstract 2239]. *Program and abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy*. Washington, DC: American Society for Microbiology; 2000.
40. Stalker DJ, Wajszczuk CP, Batts DH. Linezolid safety, tolerance and pharmacokinetics following oral dosing twice daily for 14.5 days [abstract A115]. *Program and abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy*. Washington, DC: American Society for Microbiology; 1997.

41. Chiba K, Feenstra KL, Slatter JG, Daley-Yates PT, Duncan JN, Fagerness PE, et al. Absorption, distribution, metabolism and excretion of the oxazolidinone antibiotic linezolid (PNU-100766) in the Sprague Dawley Rat [abstract A123]. *Program and abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy*. Washington, DC: American Society for Microbiology; 1998.
42. Jabes D, Candiani G, Romano G, Brunati C, Riva S, Cavaleri M. Efficacy of dalbavancin against methicillin-resistant *Staphylococcus aureus* in the rat granuloma pouch infection model. *Antimicrob Agents Chemother* 2004;**48**:1118—23.
43. Stevens D, Dotter B, Madaras-Kelly K. A review of linezolid: the first oxazolidinone antibiotic. *Expert Rev Anti Infect Ther* 2004;**2**:51—9.
44. Oramas-Shirey MP, Buchanan LV, Dileto-Fang CL, Dailey CF, Ford CW, Batts DH, et al. Efficacy of linezolid in a staphylococcal endocarditis rabbit model. *J Antimicrob Chemother* 2001;**47**: 349—52.
45. Corne P, Marchandin H, Macia JC, Jonquet O. Treatment failure of methicillin-resistant *Staphylococcus aureus* endocarditis with linezolid. *Scand J Infect Dis* 2005;**37**:946—9.
46. Diekema DJ, Jones RN. Oxazolidinone antibiotics. *Lancet* 2001;**358**:1975—82.
47. Meka VG, Pillai SK, Sakoulas G, Wennersten C, Venkataraman L, DeGirolami PC, et al. Linezolid resistance in sequential *Staphylococcus aureus* isolates associated with a T2500A mutation in the 23S rRNA gene and loss of a single copy of rRNA. *J Infect Dis* 2004;**190**:311—7.
48. Gales AC, Sader HS, Andrade SS, Lutz L, Machado A, Barth AL. Emergence of linezolid-resistant *Staphylococcus aureus* during treatment of pulmonary infection in a patient with cystic fibrosis. *Int J Antimicrob Agents* 2006;**27**:300—2.